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Side-effects of intravenous immune globulins

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SUMMARY

Intravenous immune globulin (IVIG) preparations are efficacious and safe products in use worldwide. Although rare, side-effects of IVIG may be serious, even life-threatening, and clinicians should be aware of their potential occurrence. This article summarizes most of the adverse experiences with IVIG reported in the literature since its introduction into clinical practice almost 15 years ago.

Keywords IVIG side-effects management prevention

INTRODUCTION

The clinical benefit of immune globulin prophylaxis in patients with primary antibody deficiency syndromes has been clearly established. In the past, replacement therapy was provided through intramuscular injections. In the early 1980s, highly purified monomeric suspensions of IgG for intravenous use became available and more than 10 commercial preparations of intravenous immune globulin (IVIG) are now at the disposal of the clinician. The indications for administration of IVIG have been enlarged to include transitory primary antibody deficiencies (such as low birth-weight premature babies), secondary hypogammaglobulinaemic states [as in chronic lymphatic leukaemia (CLL) or multiple myeloma], and conditions with increased susceptibility to infections (such as bone marrow transplant or the post-surgery period). In addition to its efficacy as replacement therapy, IVIG now has well-established therapeutic applications in some haematological and autoimmune diseases: IVIG preparations are used successfully in immune thrombocytopenic purpura (ITP), in Kawasaki disease, and for some desperate diseases for which there is no other efficient treatment [reviewed in refs 1 and 2]. The mechanisms of action of IVIG in these conditions, although not yet fully determined, include a reticulo-endothelial blockade, an immunomodulatory effect (by supplying anti-idiotype antibodies), and an anti-inflammatory action.

This growing usage has increased the need for high quality immune globulin products and, indeed, high-dose IVIG can be administered with only mild, self-limited side-effects. This paper reviews the most frequent adverse reactions reported with IVIG therapy from the time of its introduction into the clinic. Possible underlying causes of these reactions and their current management are described briefly.

SIDE-EFFECTS OF IVIG

The side-effects of IVIG can be separated into adverse reactions due to the relative 'impurity' of the commercial preparations (viruses, soluble substances or immunoglobulins other than IgG) and undesirable effects of their active component, the IgG. However, some of the mechanisms underlying these side-effects are speculative and probably complex. The side-effects are enumerated here according to their major manifestations, irrespective of their putative cause.

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Generalized reactions

The incidence of generalized reactions occurring during and/or after the administration of IVIG is reported to be in the range of 1–15 % (usually less than 5%). Most of them begin 30–60 min after the onset of the infusion; they are often mild, self-limited and include the following: pyrogenic reactions; minor systemic reactions such as headache, myalgia, fever, chills, low back pain, nausea and/or vomiting; vasomotor and cardiovascular manifestations marked by changes in blood pressure and tachycardia—these may be related to occasional reports of shortness of breath and chest tightness.

These reactions are generally considered to be due to aggregated immunoglobulin molecules which cause the complement system to be activated. They may be due to antigen–antibody reactions as well, or to possible contaminants or even stabilizers that may have been used during the manufacturing process. Frequently, these manifestations can be managed quite easily, sometimes just by reducing the rate of IVIG infusion or stopping it.

Far less frequently, the onset of symptoms of a generalized reaction is delayed until a few days after IVIG infusion, suggesting a type III allergic reaction [3].

Hypersensitivity and anaphylactic reactions

Severe and even fatal anaphylactoid reactions [4,5] may occur during IVIG treatment in patients with IgA deficiency; the appearance of anaphylactic shock is correlated with the presence of anti-IgA antibodies of the IgG and IgE isotypes in the patient's serum [5]. Among hypogammaglobulinaemic patients, those with combined subclass deficiency (for example, IgG2 and IgA deficiency) are more likely to develop this complication. Patients with autoimmune diseases have an increased prevalence of selective IgA deficiency when compared to normal blood donors (1/50 in systemic lupus erythematosus

versus 1/700 in a normal Caucasian population). Furthermore, anti-IgA antibodies seem to be more frequent in those IgA-deficient subjects with autoimmune diseases [6].

Seriously ill patients with a compromised cardiac function may be at increased risk of vasomotor cardiac complications, manifested by elevated blood pressure and/or cardiac failure. The kallikrein activity of some IVIG preparations has been incriminated as contributing to these adverse vasomotor reactions. Moreover, the volume of fluid delivered with IVIG (700 ml with standard preparations) is intolerable in a subset of fluid-restricted patients with congestive disease, especially at a high infusion rate.

Haemolytic anaemia

Two cases of acute Coombs-positive haemolytic anaemia developing during IVIG treatment have been published. The patients, a 30-year-old man and a 9-month-old child, were treated for ITP and Kawasaki disease, respectively [7,8]. In both cases, haemolysis mediated by antibodies to blood-group antigen could be demonstrated. When high doses of IVIG are infused, their isoagglutinin content can be sufficient to explain a Coombs-positive haemolytic anaemia. Furthermore, decreased haptoglobin levels and mild reticulocytosis have been described in normal volunteers receiving IVIG, but without any change in haemoglobin level, suggesting that clinically insignificant, well-compensated haemolysis may occur during IVIG treatment [9].

Viral contamination

Several papers published between 1983 and 1987 reported clusters of non-A, non-B hepatitis after IVIG treatment [10–13]. Hepatitis seemed to run a more severe course in hypogammaglobulinaemic patients with cirrhosis, and death by hepatic failure resulted in some of them. The mechanisms whereby some preparations (and not others during the same period) could be infectious remain unclear. They could include problems with the method of manufacture, either an isolated error in production or a basic defect in the manufacturing procedure, or an insufficient level of specific neutralizing antibody in the source plasma, allowing the presence of an excessive amount of virus. Finally, there is the possibility that the infection could be the result of non-parenteral transmission of the so-called non-A, non-B hepatitis [14].

It now appears clear that anti-hepatitis C positivity of blood products varies, depending on the country of origin of plasma donation [15]. Donors that test antibody-positive are systematically excluded. In February 1994, Baxter Healthcare Corporation, Glendale, California, USA instituted a worldwide recall of Gammagard®, its brand of IVIG, because of reports of some ten cases of possible transmission of hepatitis C. The coming months should clarify this issue and its extent. The production process for this IVIG preparation includes a chromatography procedure without any further chemical step of inactivation. As of this writing, other IVIG products currently in use have not been incriminated in hepatitis C transmission. Additional steps used in the production process of most other IVIG preparations include adjustment to pH 4, or the use of propionic acid or solvent detergent. At present, it seems cautious to use only IVIG products that have been prepared with an additional inactivation procedure.

No case of human immunodeficiency virus (HIV) seroconversion has yet been ascribed to the administration of IVIG. Furthermore, experiments in which large amounts of HIV were added to plasma before fractionation indicate that HIV is successfully eliminated during IVIG preparation.

Hepatitis B virus has not been detected in IVIG batches and the risk of its transmission is also considered negligible.

Neurological complications

As noted previously, headache is commonly reported by patients receiving IVIG; this symptom is efficiently palliated by antalgic and/or anti-histaminic drugs. Acute aseptic meningitis has been reported as a cause of recurrent IVIG-associated headaches. A 7-year-old boy treated for ITP presented with severe headache, vomiting, fever and meningism a few hours after his second infusion of IVIG [16]. A similar episode has been reported in a 2-year-old Japanese girl also treated for ITP. Seven days after IVIG infusions she experienced the same symptoms as the child just described, which were also attributed to an aseptic meningitis [17]. Two other cases have been reported in the literature [18,19]. The mechanism of this reaction remains unclear; several cases of aseptic meningitis have been associated with the use of drugs such as isoniazid and sulphamethizole or in patients with systemic lupus erythematosus taking anti-inflammatory agents.

Recently, a case of recurrent migraine after IVIG therapy has been described, suggested by the typical symptoms at presentation and the efficient prevention by propanolol before subsequent IVIG infusions. Again, the mechanism is difficult to explain [20].

Stroke as a side-effect of IVIG treatment will be discussed later.

Renal complications

Renal failure related to IVIG treatment has been reported in eight cases [21–24]. When it occurred, the best evidence for a cause–effect relationship was the close temporal association between infusion of the drug and the onset of clinical (oliguria) and biological symptoms, as well as the patients' return to pretreatment creatinine levels after stopping the drug, with the exception of a young woman who was haemodialysed and subsequently received a transplant. Renal biopsy was performed in four patients and some pathological features in three of the cases suggested a high solute load-induced damage of the proximal tubule, similar to that associated with the use of dextran or mannitol. Immunoglobulins themselves (especially large aggregates), or more likely, some component of the preparations (such as sucrose) could be responsible for this injury. The fourth case was a 39-year-old woman with mixed cryoglobulinaemia associated with a lymphoma, who had been treated specifically for hypogammaglobulinaemia and recurrent infections. The mechanism of renal damage in this case differs from the previous cases: this patient developed acute, severe, mixed cryoglobulinaemic nephropathy with evidence of antigen–antibody complex deposition after a single infusion of IVIG [24]. However, most of these patients presented with impairment of their renal function before the episode of acute degradation; IVIG treatment probably just contributed to the deterioration in renal function. Support for this conclusion comes from observations that elevated serum creatinine levels occur in patients with glomerulonephritis who receive IVIG for nephrotic syndromes

[25]. This should draw attention to the importance of screening for impaired renal function before IVIG therapy is initiated. In addition, the report of the case of acute cryoglobulinaemic renal failure after IVIG can serve as a caution against this potential complication in patients with B cell neoplasm and demonstrable serum rheumatoid factor activity.

Thrombotic events

Woodruff *et al.* reported four cases of fatal stroke in elderly patients (62–83 years old), all receiving IVIG for ITP [26]. The authors postulated that IVIG infusion could be responsible for an enhancement of adenosine triphosphate release from platelets, favouring their aggregation, as suggested by *in vitro* aggregometry studies, but these data were not confirmed by another group [27]. In those cases with ITP, the rise in platelet count during IVIG treatment could have played a role in the thrombotic event.

Recently, Reinhart & Berchtold studied the effect of high-dose IVIG on blood rheology both *in vitro* and *in vivo* [28]. Their data show that the rise in viscosity occurring after IVIG therapy can significantly impair blood flow; for this reason IVIG infusions might be sufficient to generate myocardial infarction or stroke in predisposed patients, especially elderly patients at risk of cardiovascular and thromboembolic events. However, few severe thrombotic episodes have been observed with IVIG therapy and when mentioned in case reports, the aetiological link between the treatment and frequent events in old and severely ill patients is not obvious.

Contamination of IVIG batches

Immunologically active proteins. The levels of soluble class II molecules (sHLA-DR, -DQ and -DP) in IVIG preparations appear to exceed those found in the plasma of healthy individuals, suggesting a concentration process [29]; in contrast, HLA class I molecules (A,B,C) are not detectable. Based on the total dosage of IVIG per infusion, the contaminating sHLA class II molecules may become immunogenic.

Significant levels of soluble CD4 and CD8 molecules have been found in some commercial preparations [30]. Seventeen of these were tested by enzyme-linked immunosorbent assays for the presence of proteins and cytokines such as interferon-γ (IFN-γ), tumour necrosis factor, interleukin-1 (IL-1), sIL-2 and sIL-4. Of the substances studied, only IFN-γ was present at measurable concentrations [31]. The clinical relevance of these observations remains unclear.

Anticytoplasmic antigens (ANCA). One case of uveitis has been reported in a 9-year-old hypogammaglobulinaemic patient, which was attributed to a localized vasculitis [32]. Cytoplasmic ANCA activity was detected in IVIG batches and was proposed as the cause of the vasculitis. However, the causative role for ANCA in vasculitis remains unproven [33]. Attempts to transfer the disease to animals by the same mechanism have failed. Moreover, a transient peak in serum ANCA activity has been noted after IVIG infusion, attributed to displacement of ANCA from tissue sites [34]. The young patient in the case report might have had an underlying localized vasculitis.

Miscellaneous side-effects

Many side-effects of IVIG are in the literature as sporadic case reports. Generally, the assessment of a real cause–effect relationship is sustained by a temporal association to the infusion and the absence of other obvious aetiological agents. Most of the time, no clear physiopathogenic explanation can be given.

Alopecia. Three cases of alopecia developing after infusion of IVIG have been reported [35]. The three women (aged 19, 42 and 61) were being treated for ITP and complained of diffuse alopecia up to 4 weeks after treatment. Their hair regrew within the 4 weeks following the withdrawal of IVIG. Two more cases have been reported by the IVIG manufacturers. An immunological basis for alopecia is possible, despite the negativity of immunofluorescence studies performed on the scalp biopsies of two of these patients.

Hypothermia. We saw one case of transitory hypothermia (to 35°C) in a 59-year-old CLL patient after each IVIG infusion. The pathogenesis of this observation remains obscure.

MANAGEMENT AND PREVENTION OF IVIG SIDE-EFFECTS

The management of the side-effects of IVIG is symptomatic and, in view of their mildness, they do not necessitate any aggressive treatment in most cases. Depending on the particular manifestation, drugs palliating the symptoms are antalgic, anti-pyretic, or anti-histaminic drugs; non-steroidal, anti-inflammatory agents; and/or low-dose corticosteroids.

Most adverse reactions to IVIG treatment could be reduced in three main ways: assuring the maximal purification of the product, screening the patient for factors predisposing to complications and respecting some rules of administration.

Purification of IVIG

One batch of IVIG results from processing the plasma of 3000–15 000 donors, all of whom are currently screened for hepatitis B and C, undergo HIV serology and measurement of transaminase levels. Commercial IVIG products are prepared from pooled plasma by the cold-ethanol fractionation technique based on Cohn's procedure and now in world-wide use. Once the plasma fraction II has been obtained, the immunoglobulins are stabilized by substances such as β-propionolactone. This procedure of cold-ethanol fractionation contributes to inactivation of viruses which might be present in the plasma pool, despite meticulous donor selection and the use of sensitive screening procedures. Moreover, β-propionolactone also has virucidal properties.

In addition, some manufacturers currently include a step of inactivation of lipid-enveloped viruses by a solvent detergent technique in the processing. This, concurrent with such measures as lowering the pH, raising the temperature, and increasing the incubation time during the production of IVIG, renders these products free of any major viral transmission.

The composition of each IVIG speciality is not exactly the same: they may differ in IgG subclass levels and IgA contaminants. Preparations containing very low levels of IgA should be selected for patients who present with serum anti-IgA antibodies or in emergency situations where this information cannot be obtained before IVIG treatment.

Screening of the patient

Most of the severe reactions to IVIG have been observed in patients with anti-IgA antibodies. This eventuality should be

assessed by systematic screening before any instauration of treatment, particularly in patients with hypogammaglobulinaemia or autoimmune diseases [36].

As noted earlier, the presence of rheumatoid factor activity (especially in patients with B lymphoma) or renal impairment should be investigated in any candidate for IVIG treatment.

Drug administration

Rate of infusion. The rate of IVIG infusions should be low at the beginning and increased every 15–30 min, based on the patient's tolerance. Infusion of a standard dose (e.g. 400 mg/kg) may take up to 8 h in some patients. In most cases, symptoms such as chills, fever and headache during infusion may be alleviated by lowering the rate of infusion or briefly stopping it. A phase I rate-escalation study was conducted recently in patients undergoing bone marrow transplantation and receiving 500 mg/kg of IVIG per week prophylactically, to determine the minimal period of infusion of concentrated IVIG that was well tolerated [37]. After a first infusion over a 6-h period, the 40 patients were randomized to receive the same treatment over a period of 2, 3, 4 or 5 h. The conclusion was that IVIG could be infused over a 3-h period with good tolerance, but a faster rate of infusion was poorly tolerated. This rule should be respected, particularly in patients at risk of complications (those with multi-organ failure, previous severe reactions, etc.).

Premedication. For patients with repeated reactions unresponsive to reducing the infusion rate, premedication with hydrocortisone (100 mg intravenously) or an antihistaminic drug can be considered and is generally efficacious.

CONCLUSIONS

IVIG preparations are some of the safest biological products available. Although severe adverse experiences have been reported, they are all largely anecdotal. Besides, the aetiological role of IVIG in their pathogenesis is rarely unequivocal.

The benefits of IVIG have been described for a growing number of conditions where immunoregulatory disorders are suspected and for which satisfactory alternative treatment is lacking. This harmless drug has been 'tried' and isolated therapeutic responses that are occasionally dramatic and plausible have been reported, while failures are forgotten. In contrast to the preventive indications study, few randomized placebo-controlled trials have been conducted to assess the real therapeutic impact of IVIG in conditions such as rare vasculitis, demyelinating neuropathies or severe epilepsy, which require multicentre studies. Simultaneously, the specific side-effects attributed to IVIG in those special indications could be appreciated.

To date, and because patients can be screened for anti-IgA antibodies, IVIG can be administered very safely with minimal reactions. However, this currently very expensive form of therapy should still be restricted to adequately established indications.

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